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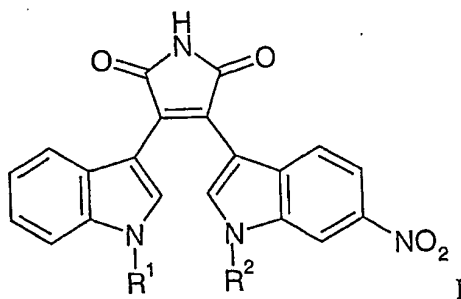
(57) Abstract: Disclosed is a process of treating a patient suffering from cancer. The process comprises administering to a patient over a period of up to about 15 days a first component and a second component. The first component consists of a pharmaceutical composition containing as an active ingredient a compound of formula (I) or a pharmaceutically acceptable salt or ester of said compound. the second component consists of a n injection solution containing as an active ingredient paclitaxel. The amount of each component in the combination is such that the combination is therapeutically effective. The components are administered concomitantly or sequentially in a three week to four week treatment cycle for as long as the tumor remains under control and the patient tolerates the regimen.

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Method of Cancer Therapy

The present invention is directed to a use of

(i) a pharmaceutical composition containing a compound of formula (I)



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and (ii) a pharmaceutical composition containing paclitaxel (commercially available as Taxol™) for the preparation of a medicament. The invention is also directed to a kit and to a pharmaceutical composition containing both of the above compounds.

10 The compounds of formula (I) below are known to be cell cycle inhibitors having potent anticancer therapeutic activity, in particular in solid tumors such as breast and colon cancers. *See, e.g.* U.S. Patent Nos. 5,057,614 and 6,048,887.

Paclitaxel is also known to be useful in cancer therapeutics. *See, e.g.*, US Patents 5,641,803 and 5,670,537 (and the references cited therein).

15 It has now been discovered that compounds of formula (I) are especially effective in cancer therapy when administered in combination with paclitaxel.

The present invention relates to a use for the preparation of medicament of a first component consisting of a pharmaceutical composition containing as an active ingredient a compound of formula (I) or a pharmaceutically acceptable salt or ester of said compound and a second component consisting of a pharmaceutical composition
5 containing paclitaxel, either concomitantly or sequentially administered. The amount of each component being such that the combination of components is therapeutically effective.

This combination of chemotherapeutic compounds is particularly useful in the treatment of cancer diseases, and more particularly useful in the treatment of breast,
10 colon, rectal, lung, uterine and prostate cancers.

It was unexpectedly found that administration of the two components in accordance with the present invention results in improved antineoplastic effects that are significantly superior to the results obtained with each compound alone. Namely, administration of the two components in accordance with the present invention resulted
15 in an improved therapeutic index (that is, superior efficacy) in comparison to either component alone without a significant increase in toxicity. Alternatively the invention permits reduction of the amount of at least one component (in comparison the amount typically given in monotherapy) while retaining a desirable therapeutic index. In preferred embodiments, the amount of both components (in comparison the amount
20 typically given in monotherapy) is reduced affording reduced toxicity while still retaining a desirable therapeutic index.

The above findings were unexpected inasmuch as similarly designed *in vitro* studies using compounds of formula (I) in combination with other antineoplastic agents (such as gemcitabine, 5-FU and carboplatin) did not produce the magnitude of effect
25 observed with compounds of formula (I) in combination with paclitaxel.

In another aspect, the invention relates to a kit. The kit comprises a first component and a second component. The first component contains one or more oral unit dosage forms of an active ingredient selected from a compound of formula (I) or a pharmaceutically acceptable salt or ester of said compound. The second component
30 contains one or more injectable unit dosage forms of paclitaxel.

FIG. 1 shows the enhanced antiproliferative activity of Compound (II) in combination with paclitaxel in a panel of cancer cell lines grown *in vitro*. Compound II and paclitaxel were tested in combination against seven different tumor cell lines. Both compounds were added, at the doses shown, 24 hours after plating the cells. The growth inhibitory effect was determined by MTT assay at time points that allowed for the untreated controls to double at least four times. Results represent the mean + the standard deviation of triplicate values from a single experiment. Similar data was obtained in at least one additional experiment.

FIG. 2 (2A, 2B and 2C) shows the enhanced antitumor activity of Compound II in combination with paclitaxel against the MDA-MB-435 breast adenocarcinoma xenograft *in vivo*.

The term "antineoplastic" means inhibiting or preventing the development, maturation or proliferation of malignant cells.

As used herein the term "concomitant" means administration of both components during the same 24 hour period, preferably within one or two hours of each other.

The term "pharmaceutically acceptable ester" of a compound of formula (I) means a conventionally esterified compound of formula (I) having a carboxyl group, which esters retain the biological effectiveness and properties of the compound of formula (I).

The term "pharmaceutically acceptable salt" of a compound of formula (I) as used herein is any conventional salt or base addition salt that retains the biological effectiveness and properties of the compound of formula (I) and which is formed from a suitable non-toxic organic or inorganic acid or organic or inorganic base. Preferred salts are cationic salts, for example, of alkali metals, especially sodium salts.

As used herein "sequential" (as in sequential administration) means that one component is administered more than twenty four hours after the other component, preferably within 2-15 days of the other component.

As used herein, "therapeutically effective" means an amount of drug, or combination or composition, which is effective for producing a desired therapeutic effect upon administration to a patient, for example, to stem the growth, or result in the shrinkage, of a cancerous tumor.

5 "Therapeutic index" is a well-recognized term of art and is an important parameter in the selection of anticancer agents for clinical trial. Therapeutic Index takes into consideration the efficacy, pharmacokinetics, metabolism and bioavailability of anticancer agents. See, e.g., J. Natl. Cancer Inst. 81(13): 988-94 (July 5, 1989).

10 "Tumor control" means that the perpendicular diameters of measurable lesions has not increased by 25% or more from the last measurement. See, e.g., World Health Organization ("WHO") Handbook for Reporting Results of Cancer Treatment, Geneva (1979).

The present invention is directed to a use of two antineoplastic components administered concomitantly or alternatively or sequentially. The first component of the
15 present invention consists of a pharmaceutical composition containing as an active ingredient a compound of formula (I), or a pharmaceutically acceptable salt or ester of said compound. The second component consists of a pharmaceutical composition containing as an active ingredient paclitaxel. The amount of each component in the combination is such that the combination is therapeutically effective to treat or
20 ameliorate a cancerous tumor. The amount of each component administered according to the present process may, but does not have to be therapeutically effective by itself. That is, this invention specifically contemplates combinations wherein the amount of compound I and/or the amount of paclitaxel in the combination is less than a therapeutically effective amount as judged by the amounts recommended in
25 monotherapy (i.e. a "suboptimal" amount).

In accordance with the present invention, administration of the two components, concomitantly or sequentially, synergistically enhances the treatment of cancer as compared to administering each component independently in monotherapy. The synergistic effect results in an improved therapeutic index as compared to either agent
30 alone while toxicity remains acceptable.

Preferably, the compound of formula (I) is administered to the patient in an oral unit dosage form, more preferably in capsule or tablet form. The second component, paclitaxel, is administered by parenteral, preferably by intravenous administration, in association with a compound of formula (I) as described herein.

5 The first component and the second component of the present invention are administered in any amount and for any duration that is effective to maintain or decrease tumor size.

In a preferred embodiment, administration of the first component and the second component occur on the first day of a 21-28 days cycle (that is, a 3 to 4 weeks repeating
10 cycle). The first component is administered daily for up to about 14 days, preferably for about 7 days, and more preferably for about 4 days. In a most preferred embodiment, the second component is administered only on the first day of the 21-28 days cycle.

The course of a preferred cycle is 21 or 28 days, though cycles anywhere between about 21 to about 28 days are also effective and contemplated. When the first
15 component is administered for about 7 to about 14 days, a 28 days treatment cycle is preferred. When the first component is administered for about 4 days, a 21 days treatment cycle is preferred. At the end of the 21-28 days of each cycle, the cycle of dosing is repeated for as long as clinically tolerated and the tumor is under control or until tumor regression. Tumor "control" is a well recognized clinical parameter, as
20 defined above. In a preferred embodiment, the cycle of dosing is repeated for up to about eight cycles.

In an alternative preferred embodiment, the second component, paclitaxel, is administered on day 1 and day 8 of a 3 weeks (21 days) or 4 weeks (28 days) cycle, preferably a 3 weeks cycle.

25 In another preferred embodiment, the second component, paclitaxel, is administered on day 1, 8 and 15 of a 3 weeks or 4 weeks cycle.

In a preferred embodiment, the amount of a compound of formula (I) is from about 800 mg/m² to about 2988 mg/m² administered over a period of up to about 14 days, more preferably from about 1068 mg/m² to about 2988 mg/m² and most
30 preferably from about 1492 mg/m² to about 2348 mg/m².

In another preferred embodiment, the amount of a compound of formula (I) is from about 800 mg/m² to about 2240 mg/m² administered over a period of up to about 4 days, more preferably from about 1120 mg/m² to about 1760 mg/m².

In a preferred embodiment, the dose intensity of the compound of formula (I) is
5 from about 267 mg/m²/week to about 747 mg/m²/week, more preferably from about 373 mg/m²/week to about 587 mg/m²/week.

In a preferred embodiment, the amount of paclitaxel is from about 135 mg/m² to about 250 mg/m² administered over a period of up to about 8 days, more preferably from about 150 mg/m² to about 200 mg/m² and most preferably about 175 mg/m².

10 In a preferred embodiment, the dose intensity of paclitaxel is from about 45 mg/m²/week to about 83 mg/m²/week, more preferably from about 50 mg/m²/week to about 67 mg/m²/week.

The dose intensity of compound of formula (I) is from about 267 mg/m²/week to about 747 mg/m²/week. The total overall dosage for the compound of formula (I) for a
15 period of up to 14 days is from about 800 mg/m² to about 2988 mg/m². A patient's body measurement in square meters ("m²"), this is a "BSA (body surface area)" measurement, typically ranges from about 1.4 m² to about 2.2 m². Thus, the total amount of compound of formula (I) to be delivered in a treatment cycle (mg) is calculated as follows:

20 [Dose intensity(mg/m²/week)] x [BSA(m²)] x [number of weeks in treatment cycle]

The foregoing amount of compound of formula (I) is divided, preferably into equal doses (though this is not required), and administered daily, as a single dose or divided into two or more doses daily, preferably twice per day, most preferably at 12
25 hours intervals ("Q12" or "BID"). The length of preferred treatment cycle is from about 3 to about 4 weeks.

Preferably, the compound of formula (I) is administered twice daily over a period of about four days. Preferred therapeutic regiments for administration of compounds of formula (I) are summarized in Tables 1 and 2 below.

TABLE 1

5 PREFERRED DOSAGE REGIMENTS OF COMPOUNDS OF FORMULA 1: 3 WEEK
CYCLE

	Dose Intensity (mg/m ² /week)	Range Total Dose/Cycle (mg/m ²)	BSA Range (m ²)	No. of days of Dosing	Individual Dose (mg/m ² BID)
Desired	267-747	800-2240	1.4-2.2	4	100-280
Preferred	373-587	1120-1760	1.4-2.2	4	140-220

TABLE 2

10 PREFERRED DOSAGE REGIMENTS OF COMPOUNDS OF FORMULA 1: 4 WEEK
CYCLE

	Dose Intensity (mg/m ² /week)	Range Total Dose/Cycle (mg/m ²)	BSA Range (m ²)	No. of days of Dosing	Individual Dose (mg/m ² BID)
Desired	267-747	1068-2988	1.4-2.2	14	38-107
Preferred	373-587	1492-2348	1.4-2.2	14	53-84

The dose intensity of paclitaxel is from about 45 mg/m²/week to about 83 mg/m²/week. The overall dosage of the second component, paclitaxel, is from about 135 mg/m² to about 250 mg/m², administered over a fifteen day period commencing on the first day of a 21-28 day cycle. In a preferred embodiment, the paclitaxel is given in one dose on the first day of a 21-day cycle. In a second preferred embodiment, the paclitaxel is given in two doses, one on the first day and one on the eighth day, of a 21-28 days cycle. In a third preferred embodiment, the paclitaxel is given in three doses, one dose each on days 1, 8 and 15 of a 28-days cycle. While the doses do not have to be equal,

they typically are. In a most preferred embodiment, the total dose of paclitaxel is administered to the patient on the first day of a 21 days cycle by approximately a three hour infusion ("i.v.").

Preferred therapeutic regiments for administration of paclitaxel are summarized
5 in Table 3 below.

TABLE 3A

PREFERED DOSAGE REGIMENTS OF PACLITAXEL - ONCE EVERY 3 WEEK
CYCLE

	Dose Intensity (mg/m ² /week)	Range Total Dose/Cycle (mg/m ²)	BSA Range (m ²)	No. of days of Dosing	Individual Dose (mg/m ²)
Desired	45-83	135-250	1.4-2.2	1 (q3w)	135-250
Preferred	50-67	150-200	1.4-2.2	1 (q3w)	150-200

10

TABLE 3B

PREFERED DOSAGE REGIMENTS OF PACLITAXEL: ONCE WEEKLY CYCLE

	Dose Intensity (mg/m ² /week)	Range Total Dose/Cycle (mg/m ²)	BSA Range (m ²)	No. of days of Dosing	Individual Dose (mg/m ²)
Desired	45-83	135-250	1.4-2.2	3 (qwx3)*	45-83
Preferred	50-67	150-200	1.4-2.2	3 (qwx3)	50-67

*qwx3= once per week for three weeks

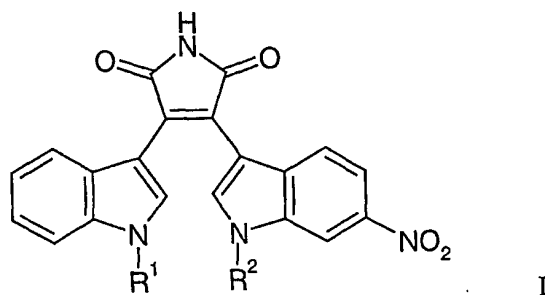
The dosage levels of each of the components may be modified by the physician to be lower or higher than that stated herein depending on the needs of the patient, and
15 the reaction of the patient to the treatment. The dosages may be administered according to any dosage schedule determined by the physician in accordance with the requirements of the patient. For example, the dosages of each of the two components

may be administered in single or in divided doses over a period of several days, or alternating daily schedules.

Preferably, four day treatment schedules are repeated every twenty one days, or as soon as permitted by recovery from toxicity, for so long as the tumor is under control and the patient tolerates the regimen or tumor regression. Seven, fourteen and fifteen day treatment schedules are preferably repeated every twenty eight days. Preferably, these treatment cycles are repeated for a total of up to about eight cycles (that is a total of about twenty four or about thirty two weeks).

In a particular embodiment, the present invention relates to the use of

- (i) a first component consisting of pharmaceutical composition containing as an active ingredient a compound of formula (I) :



or a pharmaceutically acceptable salt or ester of said compound,

wherein

- R¹ is selected from the group consisting of -H, -CH₃, and -CH₂OH, and

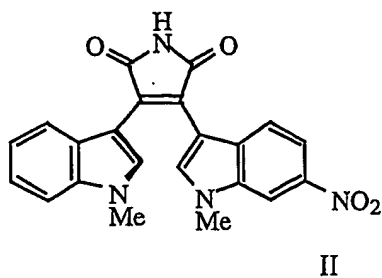
R² is -CH₃, and wherein the active ingredient of the first component is administered daily as an oral sustained release formulation for an administration period of up to about 14 days, in a total amount of from about 800 mg/m² to about 2988 mg/m² divided over the administration period; and

- (ii) a second component consisting of a pharmaceutical composition containing as an active ingredient paclitaxel, wherein the paclitaxel is administered in a total amount of from about 135 mg/m² to about 250 mg/m², over about 15 days, beginning

on the first day of the 21-28 day cycle for the treatment of a patient suffering from cancer, in particular a solid cancerous tumor.

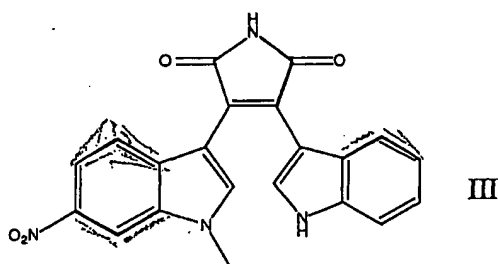
Said treatment cycle may be repeated every 21-28 days for as long as the tumor remains under control and the regiment is clinically tolerated.

5 A preferred compound of formula (I) is:

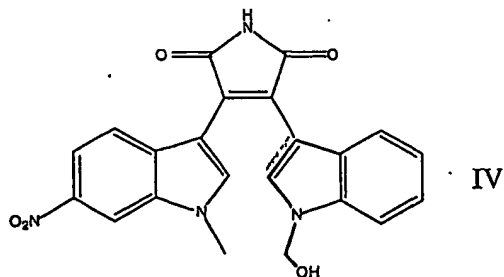


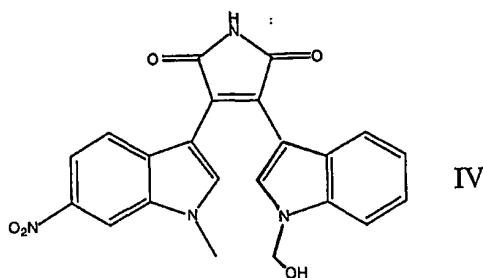
This is a known compound. See U.S. Patent 5,057,614, which is incorporated herein by reference.

10 Other preferred compounds of formula (I) are



and





Compounds III and IV above are also known compounds. See U.S. Patent 6,048,887, which is incorporated herein by reference.

The determination of tumor control (also referred to as "maintenance") or shrinkage (also referred to as "regression") is made by known processes. For example, by evaluation of patient symptoms, physical examination, X-ray, MRI or CAT scan or other commonly accepted evaluation modalities.

In a most preferred embodiment, about 180 mg/m^2 of Compound II are administered twice daily (total daily dose of about 360 mg/m^2) for 4 consecutive days commencing on day 1 of a 21 day cycle. Also on day 1 of the cycle, preferably starting at the same time as the first dose of Compound II, 135 mg/m^2 of paclitaxel are administered as a 3 hour i.v. infusion. This treatment is repeated every twenty one days, or as soon as permitted by recovery from toxicity, for so long as the tumor is under control and the patient tolerates the regimen or tumor regression. Preferably, the cycles are repeated for a total of up to eight cycles (that is twenty four weeks).

In another most preferred embodiment, 180 mg/m^2 of Compound II are administered twice daily (total daily dose of 360 mg/m^2) for 4 consecutive days commencing on day 1 of a 21 day cycle. Also on day 1 of the cycle, preferably starting at the same time as the first dose of Compound II, about 150 mg/m^2 of paclitaxel are administered as a 3 hour i.v. infusion. This treatment is repeated every twenty one days, or as soon as permitted by recovery from toxicity, for so long as the tumor is under control and the patient tolerates the regimen or tumor regression. Preferably, the cycles are repeated for a total of up to eight cycles (that is twenty four weeks).

In another most preferred embodiment; 180mg/m² of Compound II are administered twice daily (total daily dose of 360 mg/m²) for 4 consecutive days commencing on day 1 of a 21 day cycle. Also on day 1 of the cycle, preferably starting at the same time as the first dose of Compound II, 175 mg/m² of paclitaxel are
5 administered as a 3 hour i.v. infusion. This treatment is repeated every twenty one days, or as soon as permitted by recovery from toxicity, for so long as the tumor is under control and the patient tolerates the regiment or tumor regression. Preferably, the cycles are repeated for a total of up to eight cycles (that is twenty four weeks).

In another most preferred embodiment, 200 mg/m² of Compound II are
10 administered twice daily (total daily dose of 400 mg/m²) for 4 consecutive days commencing on day 1 of a 21 day cycle. Also on day 1 of the cycle, preferably starting at the same time as the first dose of Compound II, 135 mg/m² of paclitaxel are administered as a 3 hour i.v. infusion. This treatment is repeated every twenty one days, or as soon as permitted by recovery from toxicity, for so long as the tumor is under
15 control and the patient tolerates the regiment or tumor regression. Preferably, the cycles are repeated for a total of up to eight cycles (that is twenty four weeks).

In another most preferred embodiment, 200 mg/m² of Compound II are administered twice daily (total daily dose of 400 mg/m²) for 4 consecutive days commencing on day 1 of a 21 day cycle. Also on day 1 of the cycle, preferably starting at
20 the same time as the first dose of Compound II, 150 mg/m² of paclitaxel are administered as a 3 hour i.v. infusion. This treatment is repeated every twenty one days, or as soon as permitted by recovery from toxicity, for so long as the tumor is under control and the patient tolerates the regiment or tumor regression. Preferably, the cycles are repeated for a total of up to eight cycles (that is twenty four weeks).

25 In another most preferred embodiment, 200 mg/m² of Compound II are administered twice daily (total daily dose of 400 mg/m²) for 4 consecutive days commencing on day 1 of a 21 day cycle. Also on day 1 of the cycle, preferably starting at the same time as the first dose of Compound II, 175 mg/m² of paclitaxel are administered as a 3 hour i.v. infusion. This treatment is repeated every twenty one days,
30 or as soon as permitted by recovery from toxicity, for so long as the tumor is under control and the patient tolerates the regiment or tumor regression. Preferably, the cycles are repeated for a total of up to eight cycles (that is twenty four weeks).

In another most preferred embodiment; 220 mg/m² of Compound II are administered twice daily (total daily dose of 440 mg/m²) for 4 consecutive days commencing on day 1 of a 21 day cycle. Also on day 1 of the cycle, preferably starting at the same time as the first dose of Compound II, 135 mg/m² of paclitaxel are
5 administered as a 3 hour i.v. infusion. This treatment is repeated every twenty one days, or as soon as permitted by recovery from toxicity, for so long as the tumor is under control and the patient tolerates the regiment or tumor regression. Preferably, the cycles are repeated for a total of up to eight cycles (that is twenty four weeks).

In another most preferred embodiment, 220 mg/m² of Compound II are
10 administered twice daily (total daily dose of 440 mg/m²) for 4 consecutive days commencing on day 1 of a 21 day cycle. Also on day 1 of the cycle, preferably starting at the same time as the first dose of Compound II, 150 mg/m² of paclitaxel are administered as a 3 hour i.v. infusion. This treatment is repeated every twenty one days, or as soon as permitted by recovery from toxicity, for so long as the tumor is under
15 control and the patient tolerates the regiment or tumor regression. Preferably, the cycles are repeated for a total of up to eight cycles (that is twenty four weeks).

In another most preferred embodiment, 220mg/m² of Compound II are administered twice daily (total daily dose of 440 mg/m²) for 4 consecutive days commencing on day 1 of a 21 day cycle. Also on day 1 of the cycle, preferably starting at
20 the same time as the first dose of Compound II, 175 mg/m² of paclitaxel are administered as a 3 hour i.v. infusion. This treatment is repeated every twenty one days, or as soon as permitted by recovery from toxicity, for so long as the tumor is under control and the patient tolerates the regiment or tumor regression. Preferably, the cycles are repeated for a total of up to eight cycles (that is thirty-two weeks).

In another preferred embodiment, 85 mg/m² of Compound II are administered
25 twice daily (total daily dose of 170 mg/m²) for 7 consecutive days commencing on day 1 of a 28 day cycle. Also on day 1 of the cycle, preferably starting at the same time as the first dose of Compound II, 135 mg/m² of paclitaxel are administered as a 3 hour i.v. infusion. This treatment is repeated every twenty one days, or as soon as permitted by
30 recovery from toxicity, for so long as the tumor is under control and the patient tolerates the regiment or tumor regression. Preferably, the cycles are repeated for a total of up to eight cycles (that is thirty-two weeks).

In another preferred embodiment, 100 mg/m² of Compound II are administered twice daily (total daily dose of 200 mg/m²) for 7 consecutive days commencing on day 1 of a 28 day cycle. Also on day 1 of the cycle, preferably starting at the same time as the first dose of Compound II, 150 mg/m² of paclitaxel are administered as a 3 hour i.v. infusion. This treatment is repeated every twenty one days, or as soon as permitted by recovery from toxicity, for so long as the tumor is under control and the patient tolerates the regiment or tumor regression. Preferably, the cycles are repeated for a total of up to eight cycles (that is thirty-two weeks).

In another preferred embodiment, 110 mg/m² of Compound II are administered twice daily (total daily dose of 220 mg/m²) for 7 consecutive days commencing on day 1 of a 28 day cycle. Also on day 1 of the cycle, preferably starting at the same time as the first dose of Compound II, 150 mg/m² of paclitaxel are administered as a 3 hour i.v. infusion. This treatment is repeated every twenty one days, or as soon as permitted by recovery from toxicity, for so long as the tumor is under control and the patient tolerates the regiment or tumor regression. Preferably, the cycles are repeated for a total of up to eight cycles (that is thirty-two weeks).

In another preferred embodiment, 121 mg/m² of Compound II are administered twice daily (total daily dose of 242 mg/m²) for 7 consecutive days commencing on day 1 of a 28 day cycle. Also on day 1 of the cycle, preferably starting at the same time as the first dose of Compound II, 175 mg/m² of paclitaxel are administered as a 3 hour i.v. infusion. This treatment is repeated every twenty one days, or as soon as permitted by recovery from toxicity, for so long as the tumor is under control and the patient tolerates the regiment or tumor regression. Preferably, the cycles are repeated for a total of up to eight cycles (that is thirty-two weeks).

In another preferred embodiment, 134 mg/m² of Compound II are administered twice daily (total daily dose of 268 mg/m²) for 7 consecutive days commencing on day 1 of a 28 day cycle. Also on day 1 of the cycle, preferably starting at the same time as the first dose of Compound II, 175 mg/m² of paclitaxel are administered as a 3 hour i.v. infusion. This treatment is repeated every twenty one days, or as soon as permitted by recovery from toxicity, for so long as the tumor is under control and the patient tolerates the regiment or tumor regression. Preferably, the cycles are repeated for a total of up to eight cycles (that is thirty-two weeks).

In another preferred embodiment, 147 mg/m² of Compound II are administered twice daily (total daily dose of 294 mg/m²) for 7 consecutive days commencing on day 1 of a 28 day cycle. Also on day 1 of the cycle, preferably starting at the same time as the first dose of Compound II, 175 mg/m² of paclitaxel are administered as a 3 hour i.v. infusion. This treatment is repeated every twenty one days, or as soon as permitted by recovery from toxicity, for so long as the tumor is under control and the patient tolerates the regiment or tumor regression. Preferably, the cycles are repeated for a total of up to eight cycles (that is thirty-two weeks).

In another preferred embodiment, 160 mg/m² of Compound II are administered twice daily (total daily dose of 320 mg/m²) for 7 consecutive days commencing on day 1 of a 28 days cycle. Also on day 1 of the cycle, preferably starting at the same time as the first dose of Compound II, 175 mg/m² of paclitaxel are administered as a 3 hour i.v. infusion. This treatment is repeated every twenty one days, or as soon as permitted by recovery from toxicity, for so long as the tumor is under control and the patient tolerates the regiment or tumor regression. Preferably, the cycles are repeated for a total of up to eight cycles (that is thirty-two weeks).

In another preferred embodiment, 75 mg/m² of Compound II are administered twice daily (total daily dose of 150 mg/m²) for 14 consecutive days commencing on day 1 of a 28 days cycle. Also on day 1 of the cycle, preferably starting at the same time as the first dose of Compound II, 135 mg/m² of paclitaxel are administered as a 3 hour i.v. infusion. This treatment is repeated every twenty one days, or as soon as permitted by recovery from toxicity, for so long as the tumor is under control and the patient tolerates the regiment or tumor regression. Preferably, the cycles are repeated for a total of up to eight cycles (that is thirty-two weeks).

In another preferred embodiment, 75 mg/m² of Compound II are administered twice daily (total daily dose of 150 mg/m²) for 14 consecutive days commencing on day 1 of a 28 days cycle. Also on day 1 of the cycle, preferably starting at the same time as the first dose of Compound II, 150 mg/m² of paclitaxel are administered as a 3 hour i.v. infusion. This treatment is repeated every twenty one days, or as soon as permitted by recovery from toxicity, for so long as the tumor is under control and the patient tolerates the regiment or tumor regression. Preferably, the cycles are repeated for a total of up to eight cycles (that is thirty-two weeks).

In another preferred embodiment, 75 mg/m² of Compound II are administered twice daily (total daily dose of 150 mg/m²) for 14 consecutive days commencing on day 1 of a 28 days cycle. Also on day 1 of the cycle, preferably starting at the same time as the first dose of Compound II, 175 mg/m² of paclitaxel are administered as a 3 hour i.v. infusion. This treatment is repeated every twenty one days, or as soon as permitted by recovery from toxicity, for so long as the tumor is under control and the patient tolerates the regiment or tumor regression. Preferably, the cycles are repeated for a total of up to eight cycles (that is thirty-two weeks).

In another preferred embodiment, 100 mg/m² of Compound II are administered twice daily (total daily dose of 200 mg/m²) for 14 consecutive days commencing on day 1 of a 28 days cycle. Also on day 1 of the cycle, preferably starting at the same time as the first dose of Compound II, 135 mg/m² of paclitaxel are administered as a 3 hour i.v. infusion. This treatment is repeated every twenty one days, or as soon as permitted by recovery from toxicity, for so long as the tumor is under control and the patient tolerates the regiment or tumor regression. Preferably, the cycles are repeated for a total of up to eight cycles (that is thirty-two weeks).

In another preferred embodiment, 100 mg/m² of Compound II are administered twice daily (total daily dose of 200 mg/m²) for 14 consecutive days commencing on day 1 of a 28 days cycle. Also on day 1 of the cycle, preferably starting at the same time as the first dose of Compound II, 150 mg/m² of paclitaxel are administered as a 3 hour i.v. infusion. This treatment is repeated every twenty one days, or as soon as permitted by recovery from toxicity, for so long as the tumor is under control and the patient tolerates the regiment or tumor regression. Preferably, the cycles are repeated for a total of up to eight cycles (that is thirty-two weeks).

In another preferred embodiment, 100 mg/m² of Compound II are administered twice daily (total daily dose of 200 mg/m²) for 14 consecutive days commencing on day 1 of a 28 days cycle. Also on day 1 of the cycle, preferably starting at the same time as the first dose of Compound II, 175 mg/m² of paclitaxel are administered as a 3 hour i.v. infusion. This treatment is repeated every twenty one days, or as soon as permitted by recovery from toxicity, for so long as the tumor is under control and the patient tolerates the regiment or tumor regression. Preferably, the cycles are repeated for a total of up to eight cycles (that is thirty-two weeks).

In accordance with the present invention, a kit useful for treating cancer is also provided. The kit comprises a first component and a second component. The first component contains one or more oral unit dosage forms, preferably capsules, of an active ingredient, each unit containing from about 50 mg to about 200 mg of the active ingredient, wherein the active ingredient is a compound of formula (I). The second component contains a vial containing one or more unit dosage forms of paclitaxel as an active ingredient, each unit containing about 30 mg to about 400 mg.

Preferably, the first component contains a sufficient number of units so that a patient can administer up to about 2 grams per day of the active ingredient for a period of about four to 14 days and the second component contains a sufficient number of doses so that a patient can administer up to 400 mg per day for a period of about 3 days.

In another aspect of this invention, the two components herein described above are administered together with radiotherapy or alternatively together with another anticancer agent.

Further the invention concerns a pharmaceutical composition comprising a compound of formula (I), a second component consisting of paclitaxel and a pharmaceutically acceptable carrier. This pharmaceutical composition is suitable for oral administration.

Finally the present invention concerns a method of cancer therapy wherein a pharmaceutical composition containing a compound of formula (I) and a pharmaceutical composition containing paclitaxel as defined in the present invention are administering to a patient.

The present invention may be exemplified by the Examples below, which illustrate the invention without limitation.

EXAMPLES

Example 1

In Vitro Assay

Description of Tumor Cell Lines and Cultures:

5 Cell lines used for the in vitro studies were as follows: LS1034 and LS513 (both human colon carcinoma cell lines), MDA-MB-231 and MDA-MB-435 (both human mammary adenocarcinoma cell lines), MTLn3 (rat mammary adenocarcinoma cell line), H460a (human lung carcinoma), MES-SA/Dx5 (human uterine carcinoma cell line).

10 Cell lines were maintained in the designated medium (RPMI 1640 for LS1034, LS513 MDA-MB-435, MTLn3, and H460a; Dulbecco's modified medium for MDA-MB-231; McCoy's 5A medium for MES-SA/Dx5) supplemented with 10% heat-inactivated Fetal Bovine Serum (HI-FBS; Gibco/BRL, Gaithersburg, MD), 2-4 mM L-glutamine (Gibco/BRL), 50-100 units/ml penicillin and 50-100 μ g/ml streptomycin
15 (Gibco/BRL) with the following modifications.

H460a cells were grown in 20% HI-FBS (Gibco/BRL), and were grown in the absence of antibiotics. MES-SA/Dx5 cells were continuously maintained in 52 μ g/ml doxorubicin (Sigma). Unless otherwise indicated, all media are from GIBCO/BRL (Gaithersburg, MD).

20 The H460a cell line was a generous gift from Dr. Jack Roth from the M.D. Anderson Cancer Center at the University of Texas. MDA-MB-435 cells were given to us by Dr. Patricia Steeg from the National Cancer Institute upon permission of Dr. Janet Price of M.D. Anderson Cancer Center, University of Texas. MTLn3 cells were obtained from Anthony Neri, Department of Oncology, Hoffmann-La Roche Inc., Nutley, NJ. All
25 other cell lines were obtained from the American Tissue Culture Collection (ATCC), Manassas, VA.

Tissue Culture Experiment and MTT Assay. Cells were harvested in log-phase growth, suspended in tissue culture media, and 180 μ l of cell suspension containing 2×10^3 cells was added to the individual wells on a 96-well microtitre plate. Plates were

- incubated overnight at 37° C in a humidified atmosphere of 5% CO₂ before adding compounds. Paclitaxel (NaPro Biotherapeutics) and Compound II stock solutions were prepared in DMSO and diluted in complete media before adding to the appropriate wells in a volume of 10 µl. The final concentration of DMSO did not exceed 0.2%.
- 5 Plates were incubated for an additional six days at 37° C in a humidified atmosphere of 5% CO₂, at which time the antiproliferative activity of the compound combinations were assessed using the MTT assay (3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyl-2H-tetrazolium bromide) according to the procedure of Denizot and Lang (Denizot, F. and Lang, R. *J Immunol. Methods* 1986, 89, 271-277). Fifty µl of 5mg MTT(Sigma)/ml
- 10 phenol red-free RPMI 1640 supplemented with 1mM sodium pyruvate and adjusted to pH 7.2, was added to the contents of each well and the plates were incubated for an additional 3 hours. Supernatant solutions were removed by inverting and blotting the plates and 50 µl ethanol was added to each well. Plates were shaken on a Belco micro-orbital shaker for approximately 15 minutes to dissolve the formazan crystals. The
- 15 absorbance of the wells was read on a microplate spectrophotometer using 570 nm test wavelength and 660 nm reference wavelength (Bio-Tek EL320). The mean absorbance of triplicate drug-treated wells was compared to that of control wells (cells cultured without drug) and the results were expressed as percent of control using the formula:
[(Experimental - Control) / Control] x 100.
- 20 **Findings:** The antiproliferative activity of Compound II in combination with paclitaxel was evaluated *in vitro* using a tetrazolium dye assay in seven different tumor cell lines derived from a variety of cancers. Figure 1 and Table 4 show that in cell culture studies with MDA-MB-435 (breast), H460a (lung), MES-SA/dx5 (uterine), LS513 (colon), MTLn3 (breast), LS1034 (colon), and MDA-MB-231 (breast) tumor cells,
- 25 Compound II in combination with paclitaxel produced a statistically significant greater growth inhibitory effect than that produced by either compound alone at the same concentrations. The results were most dramatic in MDA-MB-435 cells, where doses that gave 10-15% growth inhibition as single agents gave greater than 80% inhibition when combined. The *in vitro* studies demonstrate dose combinations of Compound II with
- 30 paclitaxel that provide superior antiproliferative activity compared to corresponding doses of these same agents in monotherapy.

TABLE 4

Statistical comparisons for various combinations of Compound II in combination with paclitaxel *in vitro*

Cell Line	Concentration Paclitaxel(nm)	Concentration Compound II (nm)	p value
MDA-MB-435	1.0	35	<.001
MESSA/dx5	3000	100	<.001
MTLn3	3	65	<.001
LS513	30	100	.002
MDA-MB-231	2	100	<.001
LS1034	20	75	.005
H460a	2	100	.01

Table 4: The significance of combination therapy on growth inhibition was determined by comparing the antiproliferative activity of each compound used as a single agent versus the activity of the compounds when used in combination at the same concentrations. Statistical analyses were performed using the unpaired t-test. SigmaStat for Windows (Jandel Scientific, SanRafael, CA) was used for statistical calculations.

Example 2

In Vivo Assay

Mice: Female, BALB/c *nu/nu* athymic nude mice at 4-6 weeks of age were obtained from Charles River Laboratories. Animals had free access to food and water and were housed in a 12-hour light/dark cycle.

Drug Preparation and Treatment: Suspensions of Compound II were prepared by combining the drug and Pluronic F68 block copolymer at 1:9 or 1:18 ratios of drug to polymer, to prepare suspensions in the concentration range 0-10 mg/ml and 20 mg/ml respectively. The mixture was heated to between 150-190°C, and the drug was solubilized in the molten polymer to obtain a clear solution. This solution (the "glass") was then cooled to form a solid dispersion. The solid dispersion for intraperitoneal formulation was hydrated with 2.5 % dextrose solution (aqueous) by stirring at 4° C overnight to obtain a fine suspension. Paclitaxel was purchased as a powder from NaPro

Biotherapeutics, Inc. (CAS # 33069-62-4). Paclitaxel was weighed and dissolved in EtOH with thorough mixing and sonication. Cremophor (at 37° C) was added to the Paclitaxel/EtOH solution. Dilutions were made from this stock solution and the final excipient, 0.9% NaCl at 37° C, was added to each dose formulation just prior to dosing.

5 The final ratio of liquid components (EtOH, Cremophor, and saline) were 5:5:90, respectively. The experiment consisted of 16 groups which contained a vehicle group, 3 groups given Paclitaxel at 7.5, 15 and 30 mg/kg as a single agent, 3 groups given Compound II at 12.5, 25 and 50 mg/kg as a single agent and 6 combination groups of all doses of Paclitaxel and Compound II. Paclitaxel vehicle (Ethanol/Cremophor/Saline)

10 was given intra-peritoneally (i.p.), 0.5 ml, q.d., 5x/week, along with the Compound II vehicle (18% Pluronic in 2.5% dextrose solution) given i.p., 0.2 ml, twice per day (b.i.d.), 7 days/week. Compound II was administered as 0.2 ml to mice i.p., b.i.d., 7x/week, using a 1 cc syringe and a 25 gauge needle. Paclitaxel was administered to mice i.p. at 7.5 and 15 mg/kg, q.d., 5x/week while the 30 mg/kg dose was administered q.d.,

15 3x/week. Paclitaxel was administered in 0.5 ml using a 3 cc syringe and a 26 gauge needle.

Measurements: Cells were implanted into the mammary fat pad at the right flank of mice at 1.5×10^6 cells/mouse. Tumors were allowed to establish for 28 days. Mice bearing established tumors were assigned into 16 treatment groups consisting of 10

20 mice per group as follows: Tumors were measured and ranked according to size and mice bearing excessively small and large tumors were removed from consideration. The remaining mice were distributed into groups with an equal number of mice of each tumor size in each group. Tumor sizes were monitored 3 times per week by caliper measurements for three weeks. Tumor diameters were measured in two orthogonal

25 directions. Tumor volumes were calculated using the following formula:

$$\text{Tumor Volume (mm}^3\text{)} = Dxd^2/2,$$

where D is the larger diameter and d is the smaller diameter.

All mice were observed and weighed as groups, 7 times per week for three weeks. The average weight of individual mice was calculated by dividing the group weight by

30 the number of animals per group. Percent body weight change was calculated using the formula:

(Current Average Weight - Initial Average Weight / Initial Average Weight) x 100.

Statistical Analysis: Measurement of statistical significance of mean tumor volumes between treatment groups was performed using a Wilcoxon Rank Sum Test ($p < 0.05$).

5 Findings: Figure 2 and Table 5 show that significant efficacy (ranging from stasis to regression) was produced by combining low doses of Compound II and paclitaxel which were only minimally effective (e.g. slight tumor growth inhibition) as single agents. This particular combination was well tolerated, showing little evidence of enhanced toxicity. The *in vivo* studies demonstrate dose combinations of Compound II
10 with paclitaxel that provide superior therapeutic index compared to corresponding regimens using these same agents in monotherapy.

15

20

TABLE 5
TOXICITY OF COMPOUND II AND PACLITAXEL, ALONE AND IN
COMBINATION

Compound II Dose as mg/kg	Paclitaxel Dose as mg/kg	Max % Weight ^b Loss During Treatment	% Weight ^c Change at End of Treatment	Deaths/Total
0	0	NWL ^d	+ 9.5	0/10
0	7.5	NWL	+ 1.0	2/10
0	15	NWL	+ 5.8	0/10
0	30	NWL	+ 4.9	0/10
12.5	0	NWL	+ 10.0	0/10
25	0	- 4.7	+ 4.0	0/10
50	0	- 5.7	+ 7.0	3/10
12.5	7.5	- 1.7	+ 2.1	0/10
25	7.5	- 3.4	+ 6.2	2/10
50	7.5	- 14.4	NA ^e	10/10
12.5	15	- 14.6	+ 3.9	3/10
25	15	- 11.4	+ 3.3	1/10
50	15	- 17.7	NA	10/10
12.5	30	- 10.4	- 0.4	1/10
25	30	- 9.5	+ 2.8	2/10
50	30	18.8	NA	10/10

Note: During preparation of this application, it was noted that some of the mice in the above-described experiment may have been infected with *S. aureus* (based on pathologic analysis). As such, some animal deaths reported above may actually be attributable, at least in part, to the *S. aureus* infection and not to the combined treatment described above. It is also formally possible that the bacterial infection had other effects on the experimental outcomes.

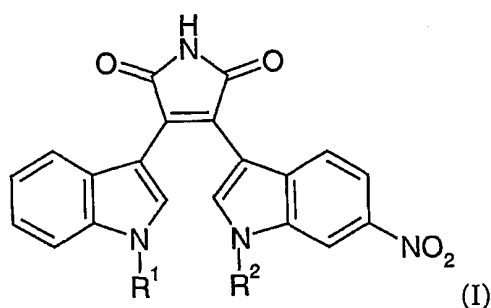
The above *in vitro* and *in vivo* data identify dose combinations of Compound II and Paclitaxel that are efficacious with minimal toxicity, and that are statistically superior in terms of antiproliferative activity and/or efficacy to corresponding doses of each agent used in monotherapy.

In contrast to the results reported above, similar studies performed using combinations of Compound II with gemcitabine, 5-fluorouracil, or carboplatin

capecitabine did not yield the same magnitude of synergistic effects. Specifically, combination effects *in vitro* with these agents did not produce the magnitude or significance of differential activity versus monotherapy observed with Compound II with paclitaxel.

CLAIMS

1. Use of a combination of a first component consisting of pharmaceutical
5 composition containing as an active ingredient a compound of formula (I)

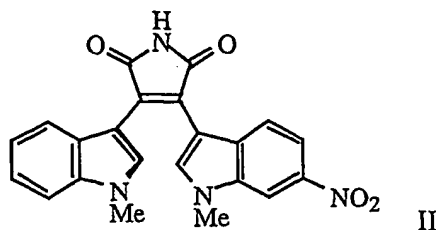


or a pharmaceutically acceptable salt or ester of said compound, wherein
R¹ is selected from the group consisting of -H, -CH₃, and -CH₂OH, and
R² is -CH₃;

- 10 and a second component consisting of paclitaxel for the preparation of a medicament.
2. The use of claim 1 for the preparation of medicaments for the treatment of cancer diseases.
3. The use according to claims 1 and 2 for the preparation of medicaments for the treatment of breast cancer, colon cancer, lung cancer, uterine cancer and prostate
15 cancer.
4. The use of any one of claims 1 to 3, wherein both components are administered concomitantly or sequentially.
5. The use of any one of claims 1 to 4, wherein the amount of compound of formula (I) in the combination is not by itself a therapeutically effective amount.
- 20 6. The use of any one of claims 1 to 5, wherein the amount of paclitaxel I in the combination is not by itself a therapeutically effective amount.

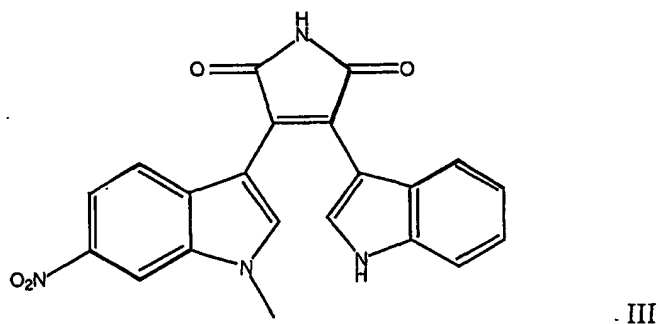
7. The use of any one of claims 1 to 6, wherein the first component is an oral unit dosage form.
8. The use of any one of claims 1 to 7, wherein the active ingredient of the first component is a compound of the formula (II):

5



or a pharmaceutically acceptable salt or ester thereof.

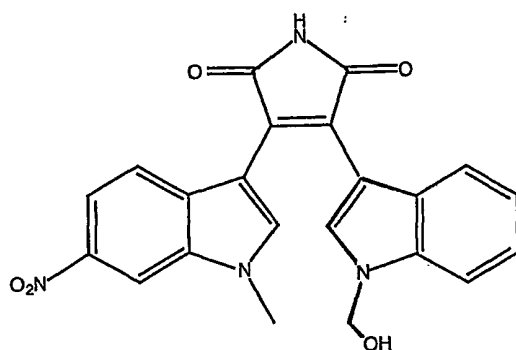
9. The use of any one of claims 1 to 7, wherein the active ingredient of the first component is a compound of the formula (III)



10

or a pharmaceutically acceptable salt or ester thereof.

10. The use of any one of claims 1 to 7, wherein the active ingredient of the first component is a compound of the formula (IV)



IV

or a pharmaceutically acceptable salt or ester thereof.

11. The use of any one of claims 1 to 10, wherein the amount of a compound of
5 formula (I) is from about 800 mg/m² to about 2988 mg/m² administered over a period
of up to about 14 days.

12. The use of any one of claims 1 to 11 wherein the amount of a compound of
formula (I) is from about 800 mg/m² to about 2240 mg/m² administered over a period
of up to about 4 days.

10 13. The use of any one of claims 1 to 12 wherein the dose intensity of the compound
of formula (I) is from about 267 mg/m²/week to about 747 mg/m²/week.

14. The use of any one of claims 1 to 13 wherein the active ingredient of the second
component is paclitaxel.

15 15. The use of any one of claims 1 to 14 wherein the amount of paclitaxel is from
about 135 mg/m² to about 250 mg/m² administered over a period of up to about 8 days.

16. The use of any one of claims 1 to 15 wherein the paclitaxel is administered on day
1 of a 21-days treatment cycle.

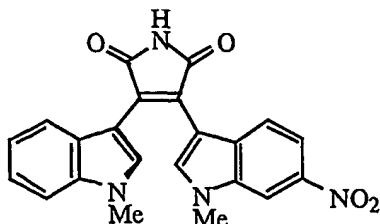
17. The use of any one of claims 1 to 16 wherein the dose intensity of paclitaxel is
from about 45 mg/m²/week to about 83 mg/m²/week.

20 18. The use of any one of claims 1 to 17, wherein the paclitaxel is administered on
days 1 and 8 of a 21-28 days treatment cycle.

19. The use of any one of claims 1 to 18 wherein the paclitaxel is administered on days
1, 8 and 15 of a 28-days treatment cycle.

20. The use of any one of claims 1 to 19 comprising administering to a patient:

(i) a first component consisting of pharmaceutical composition containing as an active ingredient a compound of formula:



5

II

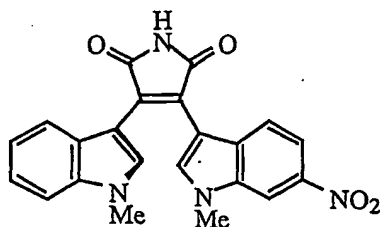
or a pharmaceutically acceptable salt or ester of said compound,

wherein the compound of formula (II) is administered in an amount of from about 76 mg/m² per day to about 214 mg/m² per day for up to about 14 days starting on the first day of a 28 days cycle, and

10 (ii) a second component consisting of an injection solution containing as an active ingredient paclitaxel which is administered in amount of from about 135 mg/m² to about 250 mg/m² on the first day of a 28 days cycle, said 28 days cycle being repeated as long as the tumor remains under control.

21. The use of any one of claims 1 to 19 comprising administering to a patient:

15 (i) a first component consisting of pharmaceutical composition containing as an active ingredient a compound of formula (II)



II

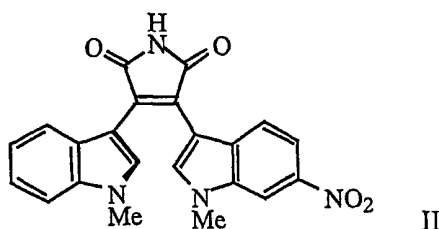
or a pharmaceutically acceptable salt or ester of said compound,

20 wherein the compound of formula (II) is administered in an amount of from about 114 mg/m² per day to about 320 mg/m² per day for up to about 7 days starting on the first day of a 28 days cycle, and

(ii) a second component consisting of an injection solution containing as an active ingredient paclitaxel which is administered in amount of from about 150 mg/m² to about 200 mg/m² on the first day of a 28 days cycle, and said 28 days cycle being repeated as long as the tumor remains under control.

5 22. The use of any one of claims 1 to 19 comprising administering to a patient:

(i) a first component consisting of pharmaceutical composition containing as an active ingredient a compound of formula (II)



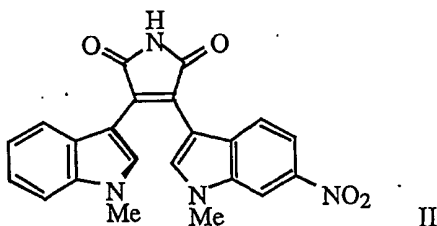
or a pharmaceutically acceptable salt or ester of said compound,

10 wherein the compound of formula (II) is administered in an amount of from about 200 mg/m² per day to about 560 mg/m² per day for up to about 4 days starting on the first day of a 21 days cycle, and

(ii) a second component consisting of an injection solution containing as an active ingredient paclitaxel which is administered in amount of from about 150 mg/m² to about 200 mg/m² on the first day of a 21 days cycle, and said 21 days cycle being repeated as long as the tumor remains under control.

23. The use of any one of claims 1 to 19 comprising administering to a patient:

(i) a first component consisting of pharmaceutical composition containing as an active ingredient a compound of formula:



20

or a pharmaceutically acceptable salt or ester of said compound,

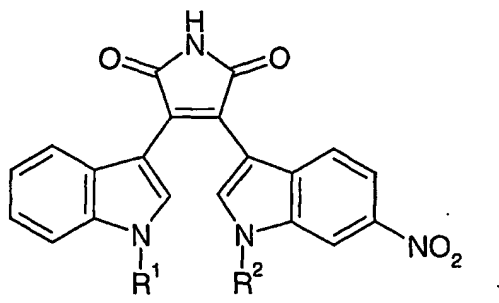
wherein the compound of formula (II) is administered in an amount of from about 200 mg/m² per day to about 560 mg/m² per day for up to about 4 days starting on the first day of a 21 day cycle, and

- (ii) a second component consisting of an injection solution containing as an active ingredient paclitaxel which is administered in amount of from about 67 mg/m² to about 125 mg/m² on the first and eighth day of a 21 days cycle, said 21 days cycle being repeated as long as the tumor remains under control.

24. The use of any one of claims 1 to 23 comprising additionally subjecting the patient to radiotherapy.

25. A kit comprising:

a) a first component containing one or more oral unit dosage forms of an active ingredient, each unit containing about 50 mg to about 200 mg of the active ingredient, wherein the active ingredient is a compound selected from formula (I)



- or a pharmaceutically acceptable salt or ester said compound, wherein

R¹ is selected from the group consisting of -H, -CH₃, and -CH₂OH, and

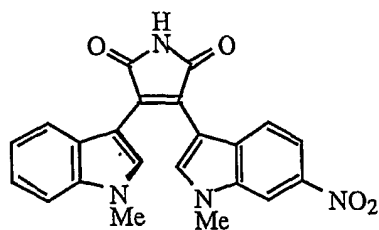
R² is -CH₃; and

- a) a second component containing a vial or series of vials, each vial containing a single injectable solution dose or multiple injectable solution doses, each dose containing as an active ingredient about 30 mg to about 400 mg of paclitaxel.

26. The kit of claim 25, wherein the first component contains a sufficient number of units so that a patient can administer about 2 grams per day of the compound of formula (I) or a pharmaceutically acceptable salt or ester of said compound for a period of about 4 to about 14 days and the second component contains a sufficient number of

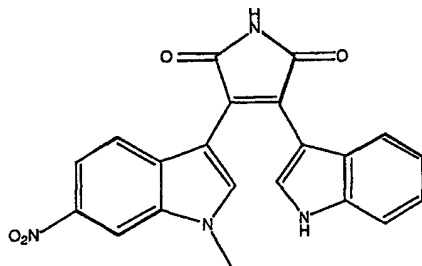
doses so that a patient can administer about 400 mg per day of paclitaxel for a period of about three days.

27. The kit of claims 25 and 26 wherein the active ingredient of the first component is



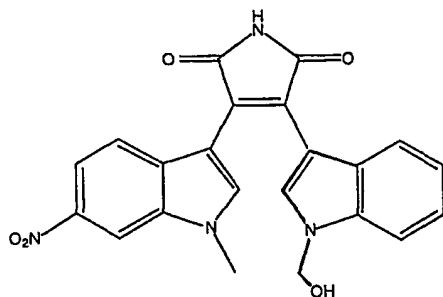
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28. The kit of any one of claims 25 to 27, wherein the active ingredient of the first component is



29. The kit of any one of claims 25 to 28, wherein the active ingredient of the first component is a compound of the formula

10



30. A method of cancer therapy wherein a pharmaceutical composition containing a compound of formula (I) and a pharmaceutical composition containing paclitaxel as defined in claims 1 to 24 are administering to a patient.

31. A pharmaceutical composition comprising a compound of formula (I), a second component consisting of paclitaxel and a pharmaceutically acceptable carrier.

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32. The novel uses, pharmaceutical compositions as well as the kits described herein before.

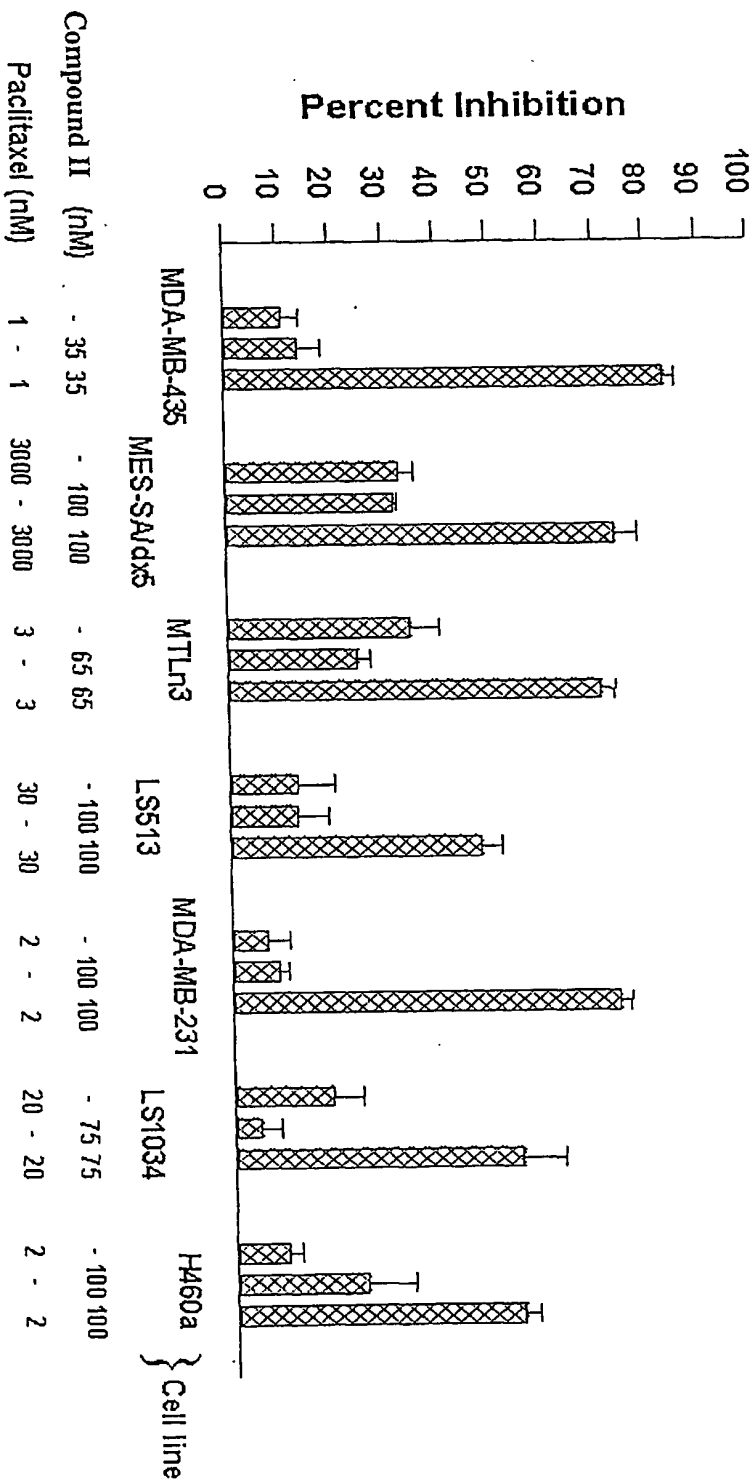


Figure 1: Compound II and paclitaxel in combination against seven different tumor cell lines

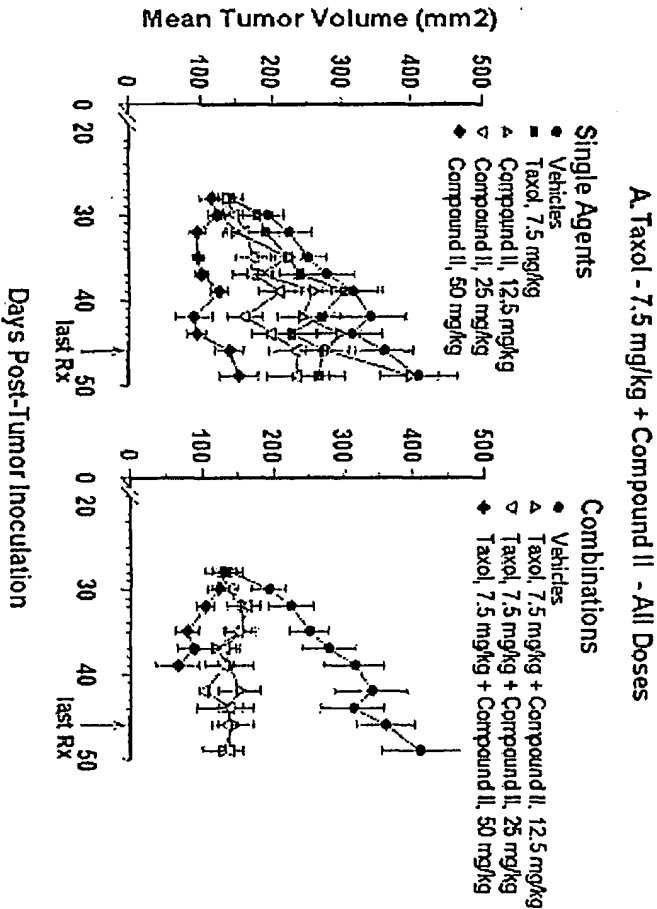


Figure 2A

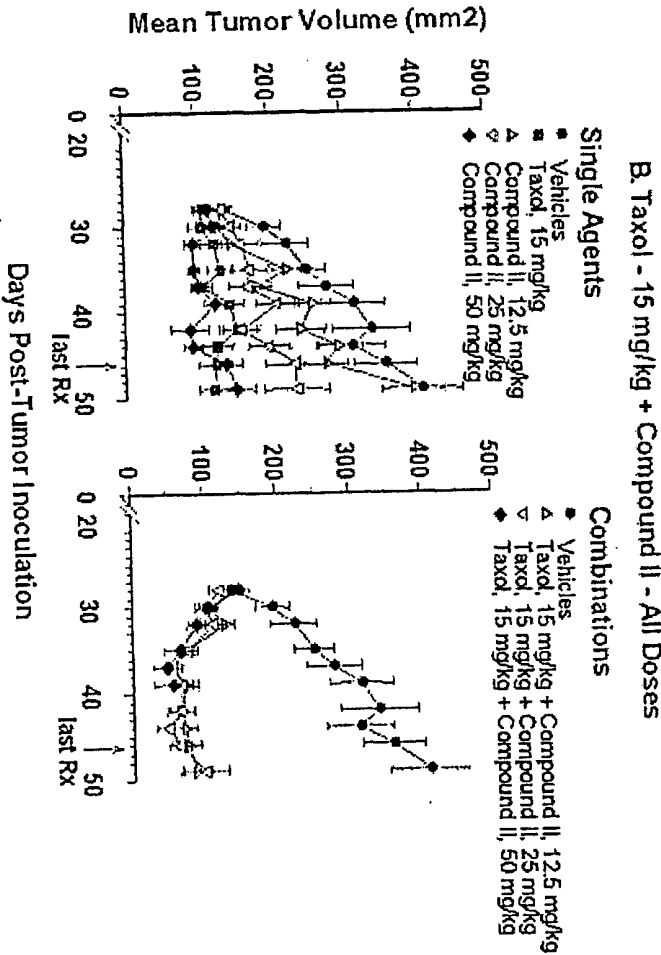


Figure 2B

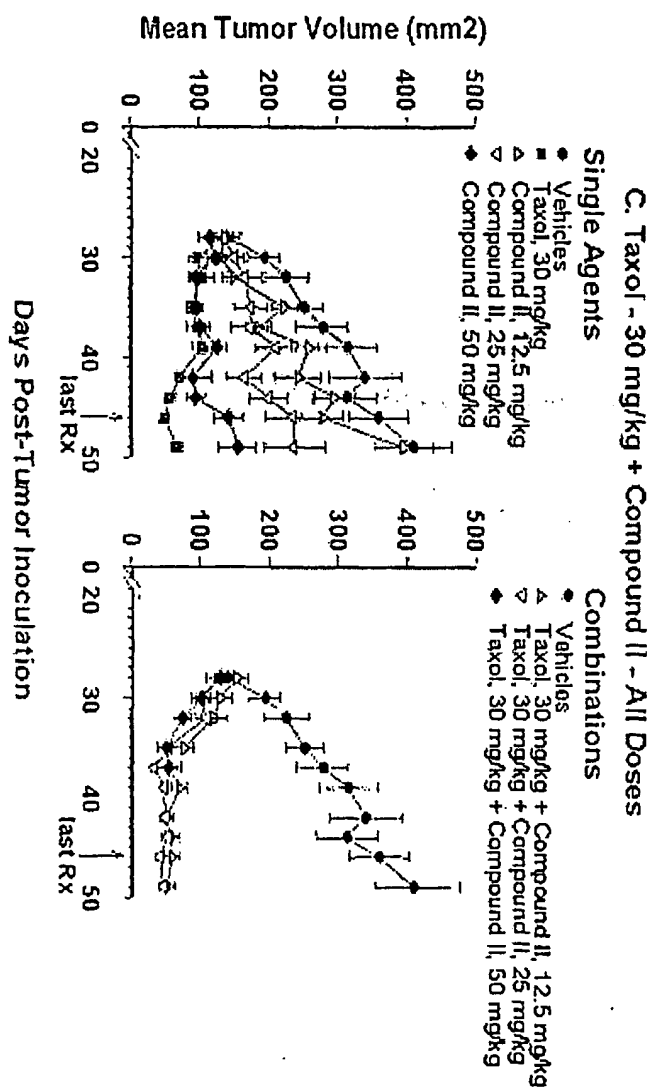


Figure 2C

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